

What is claimed is:

1. A method to determine a nucleotide sequence of a target nucleic acid, comprising
 - a) contacting the nucleic acid, or a fragment thereof, with a population of capture oligonucleotide probes bound to a substrate at a series of spot locations, to form probe-target duplex nucleic acids comprising single-stranded overhangs;
 - b) contacting the probe-target duplex nucleic acids with a population of Raman-active oligonucleotide probes to allow binding of the Raman probes to the single-stranded overhangs, wherein each Raman-active oligonucleotide probe generates a distinct Raman signature;
 - c) detecting Raman-active oligonucleotide probes that bind the template nucleic acid using Raman spectroscopy; and
 - e) identifying the location of the spot for each of the captured Raman-active oligonucleotide probes, thereby determining a nucleotide sequence of the target nucleic acid.
2. The method of claim 1, wherein each Raman-active oligonucleotide probe intrinsically generates a detectable Raman signal, or comprises a spectrally distinct Raman label or a positively-charged enhancer.
3. The method of claim 2, wherein at least one of the Raman-active oligonucleotides comprises a positively-charged enhancer.
4. The method of claim 3, wherein the positively charged enhancer is an amine group.
5. The method of claim 1, wherein at least one of the Raman-active oligonucleotides comprises a composite organic-inorganic nanoparticles
6. The method of claim 1, wherein the determined nucleotide sequence is a nucleotide occurrence at a target nucleotide position.

7. The method of claim 6, wherein the target position is a single nucleotide polymorphism position.
8. The method of claim 1, wherein the determined nucleotide sequence is a series of nucleotide occurrences at adjacent positions of a target segment.
9. The method of claim 8, wherein the target segment is less than or equal to the combined length of the capture oligonucleotide probe and the Raman-active oligonucleotide probe.
10. The method of claim 8, wherein the target segment is less than or equal to the length of the Raman-active oligonucleotide probe.
11. The method of claim 8, wherein the nucleotide sequence of the entire target nucleic acid is determined by aligning detected target sequences.
12. The method of claim 1, further comprising ligating the capture oligonucleotide probes to Raman-active oligonucleotide probes that bind to an adjacent segment of the target nucleic acid.
13. The method of claim 1, wherein the target nucleic acid is isolated from a biological source and contacted with the population of capture oligonucleotide probes, without amplification.
14. The method of claim 13, wherein 1000 or less molecules of the Raman-active oligonucleotide probe are detected.
15. The method of claim 1, wherein the substrate is a biochip.
16. The method of claim 1, wherein the Raman label is detected using surface enhanced Raman spectroscopy (SERS).

17. The method of claim 1, wherein a first population of Raman-active oligonucleotide probes are contacted with the probe-target duplex nucleic acids at a first spot of a series of spots, and a second population of Raman-active oligonucleotide probes are contacted with the probe-target duplex nucleic acids at a second spot of the series of spots, wherein the first population of Raman-active oligonucleotide probes and the second population of Raman-active oligonucleotide probes comprise at least one different oligonucleotide probe.

18. The method of claim 17, wherein the first population of Raman-active oligonucleotide probes and the second population of Raman-active oligonucleotide probes comprise at least one Raman probe with an identical Raman label bound to a different oligonucleotide.

19. A detection system comprising:

- a) a Raman spectrometer comprising a light source;
- b) a Raman active surface in optical communication with the light source; and
- c) a population of Raman-active oligonucleotide probes comprising an undetectable oligonucleotide backbone associated with a positively charged enhancer, wherein the Raman-active oligonucleotide probes are deposited on the Raman active surface.

20. The method of claim 19, wherein the positively charged enhancer is an amine group enhancer.

21. The method of claim 19, wherein the Raman active surface is a biochip.

22. A method to determine a nucleotide occurrence at a target nucleotide position of a template nucleic acid, comprising:

- a) providing a labeled oligonucleotide probe that binds to the target polynucleotide, wherein the labeled oligonucleotide probe comprises a first label and a second label, the first label affecting the Raman spectra or fluorescent signal generated by the second label based on the orientation of the first label to the second label;

b) contacting the labeled oligonucleotide probe with the target polynucleotide to form a probe-target complex; and

c) detecting the fluorescent signal or Raman spectra generated by the second label, wherein the nucleotide occurrence at the target nucleotide position affects the orientation of the first label to the second label, thereby affecting the fluorescent signal or Raman spectra generated by the second label and allowing determination of the nucleotide occurrence at the target nucleotide position.

23. The method of claim 22, wherein a fluorescent signal is detected.

24. The method of claim 23, wherein the first label and the second label are a FRET pair.

25. The method of claim 24, wherein one label is TAMRA and another label is ROX.

26. The method of claim 22, wherein a Raman spectra is detected.

27. The method of claim 26, further comprising comparing the detected Raman spectra to a database of known spectra to identify the nucleotide occurrence at the target nucleotide position of the target polynucleotide.

28. The method of claim 22, wherein the first label and the second label are located about 3-6 nm apart on the labeled probe sequence.

29. The method of claim 22, wherein a series of nucleotide occurrences for one or more target nucleotides are determined using a population of labeled probes.

30. The method of claim 29, wherein probe-target complexes are individually passed through an optical detector to read the fluorescent signal or Raman spectra generated by the probe-target complexes.

31. The method of claim 29, wherein individual probe-target complexes are individually passed through an optical detector using a microelectromechanical system having a channel that is sufficiently narrow to allow only one probe-target complex to pass.

32. The method of claim 22, wherein an alternating current (AC) is applied to the probe-target complex before detecting the probe to enhance the difference in the affect of the first probe on the second probe fluorescent signal or Raman spectra depending on whether the target polynucleotide and the labeled probe comprise complementary nucleotides at the target nucleotide position.

33. A method for detecting a nucleic acid, comprising:

- a) irradiating the nucleic acid with light, wherein the nucleic acid comprises a positively-charged enhancer; and
- b) detecting a Raman signal generated by the irradiated nucleic acid.

34. The method of claim 33, wherein the positively charged enhancer is an amine group.

35. The method of claim 33, wherein the nucleic acid does not generate a detectable signal without the positively-charged enhancer.

36. The method of claim 33, wherein the nucleic acid consists of pyrimidine residues.